DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

A JOINT MEETING OF THE

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

AND THE

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

MINUTES

Thursday, January 23, 1997

Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE
Center for Drug Evaluation and Research

CHAIRMAN

Ralph B. D'Agostino, Ph.D.

MEMBERS

Cage S. Johnson, M.D.
Theodore G. Tong, Pharm. D.
Lynn McKinley-Grant, M.D.

OTHER PARTICIPANTS

Dr. Randy Juhl
Mary Ann Koda-Kimbell

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

CHAIRMAN

Barry Massie, M.D.

EXECUTIVE SECRETARY

Joan C. Standaert

MEMBERS

Cynthia Raehl, Pharm. D.
Michael Weber, M.D.
Lemuel Moye, M.D., Ph.D.
Udho Thandani, M.D., FRCP
Robert Califf, M.D.
John DiMarco, M.D.
Marvin Konstam, M.D.
Dan Roden, M.D.C.M.

OPEN PUBLIC HEARING SPEAKERS

Darrell R. Abernethy, M.D., Ph.D.
Paul Stein, M.D.
Thomas Bryant, M.D.
Richard W. Frank
Steven Weisman, M.D.
Anthony Temple, M.D.
Fletcher McDowell, M.D.

FDA STAFF

Michael Weintraub, M.D.
Dr. Robert Temple, FDA
Dr. D. Bowen
Dr. D. Feigal

PRESENTERS

Charles Hennekens, M.D.
Rory Collins, M.D.
Colin Baigent, M.D.
Richard Peto
Stephen Kimmel, M.D.
Jeffrey Carson, M.D.
Stephen Fredd, M.D.
Mohammad Huque, Ph.D.

A joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee was called to order at 8:30 a.m., Thursday, January 23, by the chairman of the Nonprescription Drugs Advisory Committee, Ralph D'Agostino, PhD.

Advisory committee members and invited speakers were introduced and the executive secretary, Joan C. Standaert, entered the conflict of interest statement into the record. Waivers for this discussion of professional labeling for aspirin were granted to Drs. Lemmuel Moye, Barry Massie, Randy Juhl and Mary Ann Koda-Kimbell. Copies of these waivers may be obtained by writing to the FDA's Freedom of Information Office, Room 12-A-30, Parklawn Building.

Dr. Weintraub presented an award of special recognition to the Nonprescription Drugs Manufacturing Association for their assistance in helping FDA develop clear and understandable labeling for nonprescription drug products. The award was accepted by Dr. Bill Soller.

Dr. D'Agostino proceeded to the open public hearing. Six presenters were on the agenda. Dr. Darrell Abernathy spoke on behalf of the American Heart Association. He expressed the view that aspirin should be indicated for secondary prevention of heart attack in patients with documented coronary and other atherosclerosis.

Dr. Paul Stein presented on behalf of the American College of Chest Physicians. They advocated use of daily doses of 160-125 mg of aspirin for primary prevention for individuals with coronary artery disease over age 50, based on data from the Physicians Health Study. The College also recommended use of aspirin for patients with stable angina, atrial fibrillation and certain revascularizations.

Dr. Thomas Bryant presented on behalf of the Aspirin Foundation, an organization sponsored by major aspirin manufacturers. Dr. Bryant advocated an FDA recommendation for use of low-dose aspirin for primary prevention.

Mr. Richard Frank and Dr. Steven Weisman spoke on behalf of Bayer Corporation. Bayer will continue to support research and physician and consumer education about appropriate uses for aspirin. Dr. Weisman discussed the evidence from the Physician's Health Study, SPAT, ISIS-2 and the APT meta-analysis, which supported a variety of cardiovascular benefits for all levels of cardiovascular risk.

Dr, Anthony Temple, McNeil Consumer products, cautioned that with increasing numbers of patients consuming low dose aspirin, the FDA should indicate in labeling that increased risk of GI bleeding could occur when consumers ingest higher doses for fever reduction and that it might be appropriate to advise that a doctor be consulted before using increased aspirin doses.

Dr. Fletcher McDowell represented the National Stroke Association. He addressed the difference between a transient ischemic attack (TIA) and a completed stroke, where TIA could be considered the mildest completed stroke. Completed stroke carries a high risk of recurrence and Dr. McDowell advocated the use of aspirin to prevent recurrence of all degrees of completed stroke.

Dr. Michael Weintraub, Director, Office of Drug Evaluation V, presented a summary of FDA problems with the aspirin data. He described them as 4 pronged: extrapolation of data obtained from antiplatelet drugs to aspirin indications; substitution of meta-analysis results for clinical trials: the definition of high risk patients and the adverse effects of bleeding.

His remarks were amplified by Dr. Robert Temple, Director, Office of Drug Evaluation I. Dr. Temple noted that meta-analysis as a basis for primary approval has not been common. Initial approval of aspirin for use post-infarction was based on at least three specific studies that showed an effect on a combined endpoint of death plus recurrent infarction. A meta analysis was done and played a supportive role, suggesting an effect on survival, but that claim has never appeared in labeling.

Addressing the claims proposed in Dr. Hennekens petition of June 6, 1994, two seem likely to turn on extrapolation of other data. These would be patients undergoing revascularization procedures and patients deemed to be at elevated risk due to some form of vascular disease or other condition, implying an increased risk of occlusive vascular disease. Noting the types of claims currently being promoted for aspirin, Dr. Temple urged the committee to be conscious of the implications for advertizing that could result from any recommendations.

Prior to initiating formal presentations from the petitioners, Dr. D'Agostino summarized the issues the committee should address regarding the professional labeling for aspirin. The issues included extrapolation of data from minor strokes to major strokes, to atrial fibrillation and cardiac procedures, extrapolation of data from anti-platelet trials to aspirin, how to define patients at high risk and the role of meta analysis in answering these questions.

Dr. Charles Hennekens summarized the content of the citizens petition filed in 1994 . Recognizing that some data on strokes and vascular deaths remains inconclusive, the new and expanded labeling indications would approve aspirin at a maintenance dose of 75-81 mg a day for all patients who have already been diagnosed as having some occlusive arterial disease and have no special contraindications to aspirin. Dr. Hennekens estimated that underutilization or non-use of aspirin for such patients contributes to as many as 10,000 premature deaths each year in the United States.

The Anti-Platelet Trialists Collaboration (APT) published its first series of papers in the British Medical Journal in 1988. This included a meta analysis of the 25 completed trials of

aspirin, dipyridamole and/or sulfinpyrazone, conducted among 29,073 men and women with a history of MI, stroke, TIA or unstable angina. Results were significant for all patient classes as well as for a combined endpoint. Lower daily doses of aspirin were shown to be as effective as higher doses and were accompanied by reduced side effects.

ISIS-2 was a randomized trial of 17,187 patients with suspected acute MI admitted within 24 hours of onset of symptoms. Streptokinase was compared to 160 mg aspirin, streptokinase plus aspirin or placebo. The primary endpoint was 30 day mortality. This trial showed a clear benefit for the aspirin and aspirin plus streptokinase groups over streptokinase and placebo.

The ATP trials were updated in 1994 and these results were reported by Dr. Rory Collins. This data base now included 159 trials of antiplatelet therapy versus control in approximately 100,000 patients. About two thirds of these data were from trials of aspirin versus control. Individual patient report forms were obtained for analysis. The results showed no evidence that aspirin therapy was beneficial for primary prevention in low risk patients.

However in high risk patients post myocardial infarction there was a 25% reduction in vascular events, a 29% reduction in acute myocardial infarction and a 22% reduction in major vascular events including nonfatal MI, nonfatal stroke and vascular death. Adverse effects were also demonstrated. After several years of antiplatelet therapy there was an excess of one per thousand hemorrhagic strokes and 3 per thousand major noncerebal, nonfatal bleeds. On balance the benefits far outweighed the risks, particularly for patients at high risk.

Dr. Baigent summarized data published after the 1994 reanalysis. Two large international studies from Munich and China have provided evidence for aspirin's effectiveness in recurrent stroke. In the early period aspirin avoids about ten per thousand strokes in the first month and with long term use prevents another 10 per thousand per year.

The Swedish Aspirin Low-Dose Trial (SALT) randomized 1,360 patients who had a TIA, minor ischemic stroke or retinal artery occlusion within the previous six months, to aspirin 75 mg or placebo control. The primary endpoint was stroke or death. Aspirin prevented 10 per 1,000 nonfatal strokes or death.

The Swedish Angina Pectoris Aspirin Trial (SAPAT). This randomized 200 patients to SALT, who had evidence of chronic stable angina and were started on sotalol. The primary endpoint was fatal MI, with a mean follow-up of about four years. This trial showed a 30% reduction in the odds of a vascular event. These two trials taken together provide very supportive evidence for the efficacy of low dose aspirin in high risk patients. The most disappointing fact emerging from these and other trials is that aspirin was not prescribed for 24% of elderly patients upon discharge from hospital, after a vascular event.

The statistical aspect of the interpretation of the anti-platelet trials was addressed by Professor Richard Peto. He began by mentioning some of the particular problems with the Citizen's Petition as it was submitted. The petition generated some difficulties for FDA because it did not recommend a specific action. He had reduced the petition content to 7 categories of patients who might be considered for long term aspirin therapy. A copy of this proposal is appended to these minutes. Dr. Peto recommended approval of only category 1. That is aspirin, at a dose of 75-81 mg day, be approved for patients who have been diagnosed as having some occlusive arterial disease and who currently have no special contraindication to aspirin.

At the conclusion of Dr Peto's presentation Committee reviewers were encouraged to ask questions of the presenters. Dr. Califf expressed some concern about the separation of vascular death from all cause mortality. Total mortality was not the primary outcome of meta-analyses but effects of vascular mortality and total mortality were similar.

He also asked about differences in treatment effects across all categories of disease, which could not be clearly addressed from these data and found the use of the term occlusive vascular disease unclear and suggested that perhaps a more functional definition of the patient population could be developed.

Dr. Moye asked at what point the background of metaanalytic noise begins to overwhelm the signal. Dr. Hennekens responded that the magnitude of the finding for aspirin was considerable and sometimes in excess of other drugs already recommended for such cardiovascular indications.

Dr. D'Agostino noting that the meta analysis was impressive, asked for guidance on interpretation of the results. Should meta analysis replace individual trials? Because the results were so highly significant and the veracity of these data so well researched, Dr. Peto thought the results were well beyond the limits of chance.

Dr. D'Agostino also asked if a clinical argument was being put forward for equivalence of all antiplatelets and aspirin. Dr Collins responded that claims were not made that effects were the same in all categories of patients. There was clear evidence of benefit in each of the different settings and the results in the different settings reinforced each other.

Questions from other committee members were mainly concerned with isolating effects attributable to aspirin alone from the antiplatelet studies included in the meta analysis or alternatively aspirin efficacy described in other trials. The committee was also concerned about the definition of patients with peripheral occlusive disease.

At 12:35 the committee adjourned for lunch to reconvene at 1:25 p.m., when Dr. Barry Massie, chairman of the Cardiovascular and Renal Drugs Advisory Committee, assumed the chair. He introduced Dr. Stephen Kimmel who addressed the topic of aspirin and primary prevention of cardiovascular disease.

Dr. Kimmel reviewed data related to the risks and benefits of aspirin in prevention of first heart attack and stroke. He concluded that the benefit of a 17% reduction in risk of dying and a 25-30% reduction in occurrence of an event, outweighed the 1% risk of a GI bleed. Dr. Kimmel also supported the extrapolation of SAPAT data to permit an indication for arterial disease even though there were no studies of aspirin in these patients.

The adverse effects of long term aspirin were discussed by Dr. Jeffrey Carson. Studies clearly show that aspirin is associated with a dose related increased risk of GI bleeding. There was no evidence that this risk was reduced by enteric coated preparations. Dr. Carson concluded that the benefit of aspirin far outweighed the risks of GI adverse effects.

The FDA review of the 1994 Citizens Petition was presented by Dr. Steven Fredd. He wished to address the heterogeneity of the antiplatelet agents and underlying "occlusive diseases" contained in the meta-analysis and the development of direct randomized evidence that may support a uniform effect in various occlusive diseases. He concluded that aspirin could be recommended for use in patients with chronic stable angina but that the use of aspirin alone to prevent periprocedural events was not established. Dr. Fredd also concluded that claims for Peripheral Vascular Disease was not established by data from use in patients with Peripheral Vascular Disease.

At this time the committee began consideration of the questions asked by the FDA. A copy of these questions is appended to these minutes.

The committee unanimously recommended that the results of the SAPAT trial supported the conclusion that aspirin was beneficial for prevention of vascular events in patients with stable angina pectoris. The second question was revised to ask, "In major completed stroke is their evidence that aspirin prevents recurrent vascular events including stroke, myocardial infarction and vascular death. The committee recommended approval if the analysis of the recently completed ESPS-2 trial supported the claimed efficacy endpoint.

The committee discussed possible labeling for aspirin use in revascularized patients. They supported an indication for patients who have had revascularization for symptomatic or clinically manifest coronary disease (CABG and PCTA). The last clinically manifest vascular disease to be discussed was peripheral vascular disease. The difficulty with this indication was the extrapolation of results from non-aspirin anti-platelet trials to the aspirin indication. Results from aspirin studies alone were weak.

Some members were convinced that generalizations could be based on the view that all types of vessel disease were the result of an atherosclerotic process. Diagnosis of the severity of this disease was limited by the fact that many of these patients were asymptomatic because their coronary artery disease prevented them from exertion. The committee recommended 11-4 that professional labeling should not include an indication for use in peripheral vascular disease because the evidence did not meet usual standards for approval.

Dose and duration were also addressed. Evidence indicates that doses of 75-81 mg of

aspirin will produce complete inhibition of platelet-dependent cyclooxygenase for the life of the platelet over a two day period. Higher doses must be used to produce a rapid effect. Side effects also appeared to be dose related. Differing doses have been demonstrated to have efficacy in differing disease states. This information should be provided to the health care professional who advises the patient. The meeting was then adjourned at 4:30 p.m..

I certify that I attended the January 23, 1997, joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Ralph D'Agostino,PhD.,
Chairman Nonprescription Drugs Advisory Committee

Barry Massie, M.D., Chairman
Chairman Cardiovascular and Renal Drugs Advisory Committee

Joan C. Standaert M.S.
Executive Secretary, Cardiovascular and Renal Drugs Advisory Committee

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: JOINT MEETING OF THE NONPRESCRIPTION DRUGS AND CARDIOVASCULAR and RENAL DRUGS ADVISORY COMMITTEES

DATE OF MEETING: 01/23/97

QUESTIONS

Questions for the Joint Committee of the
Nonprescription Drugs Advisory Committee and the
Cardiovascular and Renal Drugs Advisory Committee

BACKGROUND INFORMATION

Current Agency Status of Professional Labeling Indications For Aspirin:

1. Indications Accepted:

   a. TIA
   b. Recurrent Myocardial Infarction
   c. Unstable Angina Pectoris
   d. Suspected Acute Myocardial Infarction
   e. Minor Ischemic Stroke

2. Indication Not Accepted:

   - Prevention of First Myocardial Infarction in Healthy People

3. Indication Under Consideration:

   - Stable Angina Pectoris

4. Additional Indications Requested by the Petition:

   a. Patients undergoing coronary, cerebral or peripheral arterial revascularization procedures (CABG, PTCA, carotid endarterectomy, peripheral artery grafts, surgically created peripheral arterial fistula, peripheral angioplasty).
   b. Patients with chronic non-valvular atrial fibrillation.
   c. Patients requiring hemodialysis access with a fistula or shunt.
   d. Major completed stroke
   e. Other patients deemed to be at elevated risk due to some form of vascular disease or other condition implying an increased risk of occlusive vascular disease.

QUESTIONS

1. In your opinion, do the SAPAT data support the conclusion that aspirin is beneficial in the primary prevention of non-fatal myocardial infarction in patients with stable angina pectoris?

2. In the past, the Agency has required specific clinical data to support each indication (e.g., prevention of stroke, TIA, MI) for aspirin. In your opinion, can extrapolations be made from the available data on aspirin to patient populations which have not been studied in formal clinical trials but are at risk for occlusive vascular events? (Revised)

3. If the answer to question #2 is yes, which populations listed under Background Information #4 would you specify, which not, and why?

4. If the answer to question #2 is yes and extrapolations can be made, how would the dose and duration of treatment for these patient populations and indications be determined?

5. Please comment on the use of data from studies of anti-platelet drugs other than aspirin to approve new professional uses of aspirin.

6. Please comment on the use of aspirin in patients who have not had a signal event (symptom or sign) but are considered to be at high risk for the development of occlusive vascular disease (i.e., family history, diabetes, hypercholesterolemia, etc). Define high risk.

Open Public Hearing Speakers

Am. College of Chest Physicians	Dr. Paul Stein	In support, based on 4th ACCP Consensus Conference on Antithrombotic Therapy
National Stroke Assn.	Dr. Fletcher McDowell	In Support
Bayer Corp.	TBA	In support
McNeil Corp	Dr. Anthony Temple	In support
Aspirin Foundation	Dr. Thomas Bryant	TBA
Am. Heart Assn.	TBA	In support
Am. College of Cardiology	Dr. Noel Bairey Merz (If not acting as Industry Representative for NDMA)	TBA

FROM: Joan C. Standaert, Executive Secretary, Cardiovascular and Renal Drugs Advisory Committee

TO: Director, HFD-1

SUBJECT: 79th meeting, Cardiovascular and Renal Drugs Advisory Committee, jointly with Nonprescription Drugs Advisory Committee, January 23, 1997. INFORMATION ALERT MEMORANDUM

The joint advisory committees convened to discuss a citizen's petition from the Aspirin Strategy Group, seeking broadened indications for professional labeling for aspirin to include anyone at risk for heart attack and stroke. The committees heard presentations from interested professional organizations and corporations, in open public hearing and in open session from the Aspirin Strategy Group.

The committees unanimously recommended that results from the Swedish Angina Pectoris Antiplatelet Trial supported the benefits for low-dose aspirin in patients with stable angina pectoris. The committees also unanimously recommended that low-dose aspirin be extended to patients with arterial revascularization procedures, i.e., CABG or PTCA. The committees gave a conditional recommendation for the use of aspirin in patients with ischemic stroke pending the agency's acceptance of data from the European Stroke Prevention Trial 2 (ESPS2).

The committees recommended that available data on aspirin not be extrapolated to patients with occlusive peripheral arterial vascular disease (11 no, 4 yes).

Ten questions, of which the first is much the most important, that could be put to the cardio-renal advisory committee on 23 January 1997, at the hearings on the 1994 citizens' petition on aspirin. Note: The full 1994 citizens' petition to FDA is several hundred pages long. Even if members do not have time to scrutinise all of it in full detail, it would be helpful if, before considering these questions, they were able to scrutinise in it the text and, particularly, the Discussion (p.93) of Part I of the 1994 APT report (BMJ 308: 81-106: copy attached).

ASPIRIN: CONTRAINDICATIONS, INDICATIONS AND UNCERTAINTIES

Neither the petitioners, nor the FDA, wish to recommend the use of aspirin by people who are not already at appreciable risk of occlusive vascular disease, because if the current risk without aspirin is small then any benefits of aspirin would currently be small, and may well not justify the small but definite increase in the risk of cerebral haemorrhage or other major bleeding. Conversely, neither the petitioners, nor (presumably) the FDA, would want to perpetuate the under-use of aspirin in those who are already at such high risk of occlusive vascular disease (i.e. myocardial infarction or occlusive stroke) that the risk reduction from aspirin greatly exceeds any hazard. Finally, both would agree that there are some categories of patient (including the large majority of those people who do not yet have evidence of occlusive arterial disease) where the balance of risk and benefit remains unclear, and so no professional labelling can yet be justified. What is needed is advice from the committee as to how, in practical terms, such categories can be defined clearly enough for unambiguous and appropriate professional labelling to follow quickly.

NEED FOR CLEAR CATEGORIES: NOT TOO NARROW, NOR TOO WIDE

One problem with the 1994 citizens' petition is that the category of patients for which professional labelling is requested varies slightly from place to place in the document (e.g. on page 1 it is all who are at high risk for occlusive vascular events, irrespective of the reason for this; on page 2 it includes only those who are at high risk due to

prior cardiovascular disease history; on page 4 it includes haemodialysis patients with a recent fistula or shunt, irrespective of their risk of occlusive vascular disease). Perhaps, therefore, it would be appropriate for the first questions to the committee to be concerned with exactly which category of patients to treat. For example:

QUESTION I: PRE-EXISTING OCCLUSIVE ARTERIAL DISEASE
Is aspirin (at a maintenance dose of at least 75 or 81 mg/day: see below) indicated for all patients who have already been diagnosed as having had some occlusive arterial disease, and who currently have no special contraindication to low-dose aspirin?

Notes:

(1) This is the key category; it is simple to state and simple to understand, yet it includes the great majority of those who could, on present evidence, be claimed to benefit substantially, and it does not appear to include any for whom substantial concerns about inappropriate over-treatment can be justified.

(2) Question I implies treatment for stable angina, unstable angina, suspected or definite acute myocardial infarction, a previous history of myocardial infarction, transient cerebral ischaemia, occlusive acute stroke, any current or previous history of occlusive stroke, coronary, carotid or peripheral arterial occlusion, and both perioperative and longer-term treatment for those who have had arterial grafts, angioplasty or other arterial procedures.

(3) The category of patients in Question I differs from that in the 1994 citizens' petition in that it does **not** include those who have not yet developed occlusive arterial disease but who are at substantial risk of doing so in the near future because of severe diabetes, severe hypertension, very high blood cholesterol (or other lipid abnormalities), or renal failure (even though haemodialysis patients

have death rates from occlusive vascular disease that are an order of magnitude greater than those of the general population).

(4) Question I does not specify whether patients who have been hospitalised for acute occlusive stroke should start aspirin immediately after their CT scan, or whether they should wait until the time of hospital discharge. (Randomised evidence on 33,000 acute stroke patients was, however, presented at the 1996 international stroke conference at Munich that strongly indicated that the earlier aspirin starts in hospital the better).

(5) Although there is convincing randomised evidence that in certain types of patient (e.g. those undergoing maior surgical procedures) aspirin can substantially reduce the incidence of deep vein thrombosis and can approximately halve the incidence of pulmonary embolism (see Part III of the 1994 APT overview, which is provided in the citizens' petition), venous thromboprophylaxis should, to avoid confusion, be considered only on some other occasion, and is not discussed at all in these proposed questions.

Questions II-VII then consider possible extensions of the main indication in Question I, and the remaining questions (VIII, IX & X) then relate to other matters.

QUESTION II: DIABETICS without evidence of occlusive arterial disease
Is aspirin likewise (i.e. as in Question I) indicated in middle or old age for the prevention of occlusive vascular disease in those who are being treated medically for diabetes, but who have not yet been found to have any occlusive arterial disease?

QUESTION III: RENAL PATIENTS without evidence of occlusive arterial disease
Is aspirin likewise indicated in middle or old age for the prevention of occlusive vascular disease in those who are being treated for renal insufficiency, but who have not yet been found to have any occlusive arterial disease? (Note: This question is not related to the maintenance of haemodialysis shunt patency.)

QUESTION IV: ATRIAL FIBRILLATION without evidence of occlusive arterial disease
Is aspirin likewise indicated in middle or old age for the prevention of occlusive vascular disease (especially stroke) in those with chronic atrial fibrillation, but who have not yet been found to have any occlusive arterial disease?

QUESTION V: HYPERTENSIVES without evidence of occlusive arterial disease
Is aspirin likewise indicated in middle or old age for the prevention of occlusive vascular disease in those who are being treated for hypertension, but who have not yet been found to have any occlusive arterial disease?

QUESTION VI: HYPERLIPIDEMICS without evidence of occlusive arterial disease
Is aspirin likewise indicated in middle or old age for the prevention of occlusive vascular disease (especially myocardial infarction) in those who are being treated for elevated blood cholesterol, but who have not yet been found to have any occlusive arterial disease?

QUESTION VII: <u>ANY</u> OTHER HIGH-RISK CATEGORY without evidence of occlusive arterial disease? (This could include, or go beyond, II-VI)
Among those who have **not** yet been found to have any occlusive arterial disease, can **any** category of patient be defined, in a way that might be clear enough to lead to professional labelling, where aspirin is clearly indicated for the prevention of myocardial infarction, occlusive stroke or other occlusive arterial disease? (Note: This question excludes the use of aspirin for the prevention of deep vein thrombosis.)

General note: After discussing the trial evidence and some general statistical principles, an uncomplicated, unqualified positive answer to Question I will be strongly recommended by the petitioners. But, Questions II to VII are more open to differences of opinion, and the current answers to them may well be modified by further research.

Questions on other subjects

QUESTION VIII: SEX, AGE, BLOOD PRESSURE, DIABETES

Among those who are to receive low-dose aspirin for the prevention of myocardial infarction, occlusive stroke, or other occlusive arterial disease, should any be denied treatment on the grounds of gender, age, blood pressure or diabetes? (Probably not: see Figure 7 on page 92 of the 1994 APT report.)

QUESTION IX: CONTRAINDICATIONS TO ASPIRIN USE

Should any specific contraindications be listed (e.g. definitely known allergy to aspirin, recent intra-cranial bleed, current gastric bleed or ulcer), and should these be clearly specified as **relative** contraindications?

Note: In circumstances where the immediate benefits of aspirin are substantial (e.g. acute MI), it is important to forego them only for **really major** contraindications; even a currently active gastric ulcer may be relatively less important, and a past history of ulceration would almost certainly be so: see Figure. (As an example of inappropriate professional labelling of possible side-effects, before the ISIS-2 trial one stated "contraindication" to streptokinase on the data sheet was the use of aspirin!)

QUESTION X: ASPIRIN DOSAGE

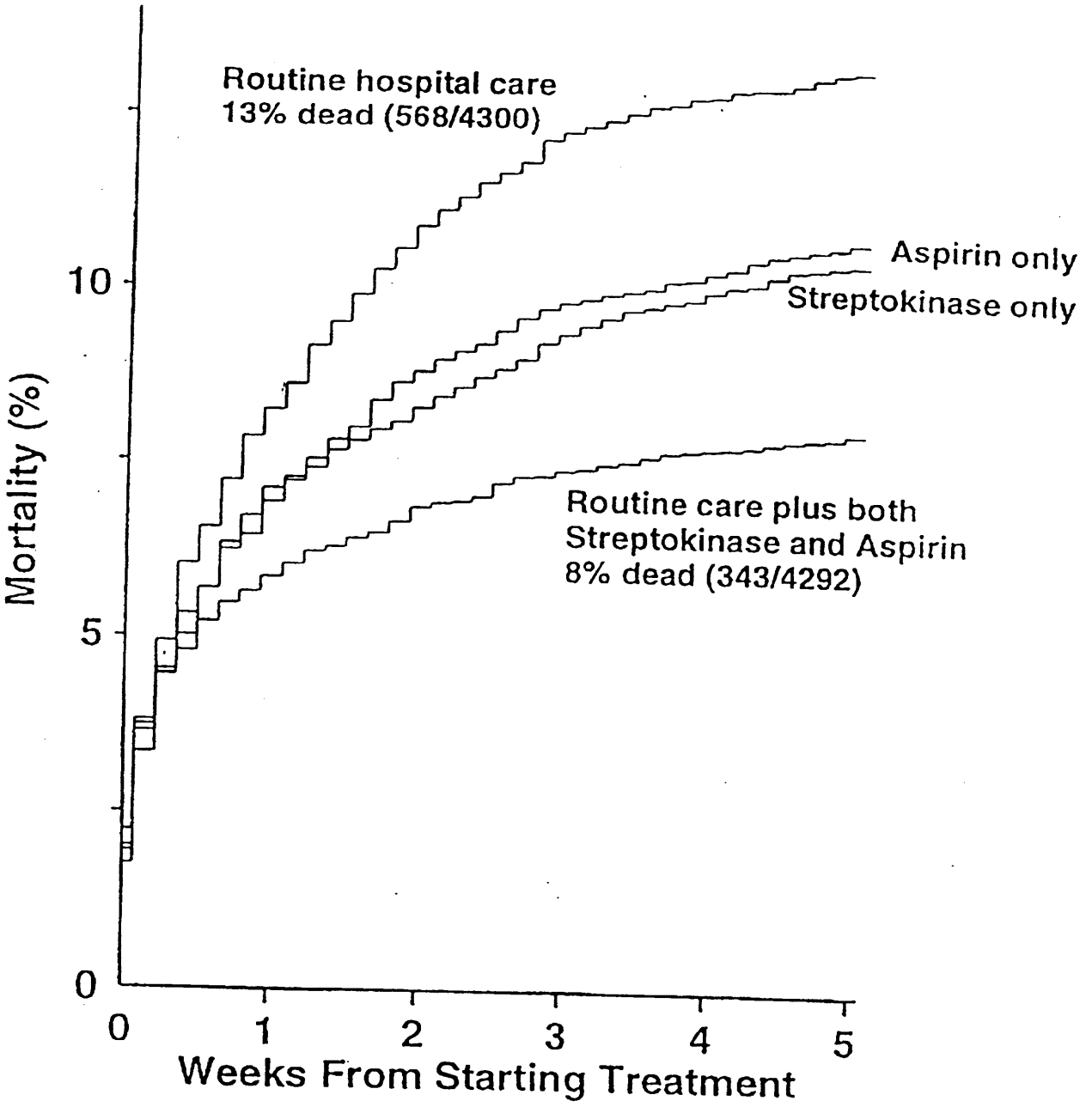
In the light of the 1994 APT report and the additional trials since then, does the committee concur with the conclusion on the final page of the Discussion of the 1994 APT report that "Medium-dose aspirin (75-325 mg/day) is the most widely tested ..... regimen, and no other regimen appeared significantly more effective [in patients with some pre-existing occlusive arterial disease] at preventing myocardial infarction, stroke, or death"?

Notes:

(1) Question I suggested a **maintenance** dose of at least 75 or 81 mg/day, but did not specify what the **initial** dose should be. In most medical circumstances no special initial dose is needed, but in acute ischaemic conditions treatment should begin with enough aspirin to guarantee that a virtually complete effect is obtained rapidly after the first dose, which should therefore be at least 162 mg, as in ISIS-2, or even 250, 300 or 325 mg, rather than, for example, 75 or 81 mg.

(2) In various parts of Western Europe, aspirin doses of 75, 100, 150, 250 or 300 mg may be conveniently prescribable, while in North America doses of 81, 162 or 325 mg may be conveniently prescribable. Some trials have demonstrated clearly significant benefits with 75 mg/day, but substantially lower doses have been much less extensively studied for their effects on clinical endpoints and they may not suffice to maintain full inhibition of platelet cyclo-oxygenase. Thus, although the 1994 citizens' petition suggests recommending aspirin at a dose of "at least 81 mg/day", a more appropriate recommendation might be "at least 75 or 81 mg/day". Higher doses are more gastrotoxic, and have not been reliably shown to be more effective than 75-325 mg/day: the current recommendation of 1300 mg/day for stroke cannot be justified (see Discussion of 1994 APT report).

(3) If the committee cannot agree on which dose to recommend, then it is important not to let this prevent recommending that aspirin should be used for an appropriately wide range of patients. (It would, for example, be possible for the committee to recommend the use of aspirin "at the lowest effective dose", or "at an appropriate dose", leaving FDA to decide subsequently what this implies.)



Cumulative Vascular Mortality From Days 0 to 35 in the ISIS-2 Trial.

17,187 patients randomly assigned within 24 hours of the onset of suspected acute myocardial infarction to receive (i) placebo infusion and placebo tablets, (ii) placebo infusion and 162.5 mg aspirin daily for one month, (iii) 1,500,000 units of streptokinase infusion over one hour and placebo tablets, or (iv) both